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ORIGINAL ARTICLE

Evolution of the surgical management of perihilar cholangiocarcinoma in a Western centre demonstrates improved survival with endoscopic biliary drainage and reduced use of blood transfusion

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Abstract

Background: Perihilar cholangiocarcinoma (PHCCA) remains a surgical challenge for which few large Western series have been reported. The aims of this study were to investigate the results of surgical resection for PHCCA and assess how practice has evolved over the past 15 years.

Methods: A prospectively maintained database was interrogated to identify all resections. Clinicopathological data were analysed for impact on survival. Subsequently, data for resections carried out during the periods 1994–1998, 1999–2003 and 2004–2008 were compared.

Results: Eighty-three patients underwent resection. Trisectionectomy was required in 67% of resections. Overall survival was 70%, 36% and 20% at 1, 3 and 5 years, respectively. Size of tumour, margin (R0) status, lymph node status, distant metastasis, tumour grade, portal vein resection, microscopic direct vascular invasion, T-stage and blood transfusion requirement significantly affected outcome on univariate analysis. Distant metastasis ($P = 0.040$), percutaneous biliary drainage ($P = 0.015$) and blood transfusion requirement ($P = 0.026$) were significant factors on multivariate analysis. Survival outcomes improved and blood transfusion requirement was significantly reduced in the most recent time period.

Discussion: Blood transfusion requirement and preoperative percutaneous biliary drainage were identified as independent indicators of a poor prognosis following resection of PHCCA. Longterm survival can be achieved following the aggressive surgical resection of this tumour, but the emergence of a clear learning curve in our analyses indicates that these patients should be managed in high-volume centres in order to achieve improved outcomes.

Keywords

cholangiocarcinoma < liver, resection < cholangiocarcinoma, outcomes < cholangiocarcinoma

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Introduction

Cholangiocarcinoma, a primary tumour of the biliary epithelium, accounts for 3% of all gastrointestinal malignancies, but has a dismal prognosis.[1] Cholangiocarcinoma can occur at any location in the biliary tree, but is most commonly (60–70%) evident at the confluence of the hepatic ducts; this manifestation is termed 'hilar cholangiocarcinoma'.[2] Hilar cholangiocarcinoma was first described in detail in 1965 by Gerald Klatskin and hence these tumours are often termed 'Klatskin tumours'.[3] More recently, the term 'perihilar cholangiocarcinoma' has been used to include both intra- and extrahepatic cholangiocarcinomas affecting the hepatic hilum as they are managed similarly.[4] This paper considers both

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intra- and extrahepatic examples of this cholangiocarcinoma under the umbrella term 'perihilar cholangiocarcinoma' (PHCCA).

Perihilar cholangiocarcinoma tends to present late for several reasons. The unobstructive lateral extension of the tumour combined with the detergent properties of bile result in the late occurrence of the complete obstruction of the bile duct, which causes jaundice, the most common form of presentation.[5] This late presentation combined with the intimate relations of this tumour with the portal vein, hepatic arteries and liver make PHCCA a surgical challenge. Surgery remains the only curative therapy for patients with PHCCA, although chemotherapy, radiotherapy and photodynamic therapy are sometimes useful as adjuncts to surgical resection or as palliative therapy.[6–8]

The aim of this study was to assess the results of surgical resection for PHCCA over the last 15 years in a large Western hepatobiliary tertiary referral centre and to establish which factors significantly affect survival. Furthermore, by dividing the data into three datasets for three consecutive time periods, we investigated how practice has evolved and what impact this has had on patient outcomes.

Materials and methods

Patient selection

Patients who underwent a first liver resection for PHCCA between January 1994 and December 2008 were identified from a prospectively maintained database containing all liver and biliary resections carried out at St James's University Hospital, Leeds, UK. Demographic data assessed included information on patient age, gender, mode of presentation, pre-resection interventions and investigations. Other data included operative findings, surgical techniques, blood transfusion requirements, histopathology, and morbidity and mortality. Perioperative mortality was defined as death as an inpatient or within 30 days of surgery. Patients' notes were checked for database accuracy and follow-up visits were arranged for follow-up completion. In addition to an analysis of the entire group, datasets for three 5-year time periods were assessed (Period 1: 1994–1998; Period 2: 1999–2003; Period 3: 2004–2008) to investigate how practice and outcomes have evolved.

Preoperative workup

Contrast-enhanced magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) and magnetic resonance angiography (MRA) were used to assess the extent of the tumour and its relationship to biliary and vascular structures. If jaundice was present, a biliary drainage procedure was performed. Endoscopic biliary drainage (EBD) was the preferred mode of drainage, but percutaneous transhepatic biliary drainage (PTBD) was often carried out prior to referral and was employed when EBD was not possible. Early in the experience, preoperative biliary drainage was used only in patients with a serum bilirubin level >300 μmol/l (17.54 mg/dl), but jaundice was quickly recognized as an adverse risk factor and thus for the last 10 years all patients with a serum bilirubin level >50 μmol/l (2.92 mg/dl) have been drained. Current practice is to drain only the planned liver remnant except in cases of bilateral biliary sepsis, when both lobes require to be drained. Computed tomography (CT) of the chest, abdomen and pelvis was used to assess potential sites of metastatic disease. Diagnostic staging laparoscopy was employed routinely to assess for peritoneal metastases. Since 2006, positron emission tomography (PET) has also been used to assess for extrahepatic disease. Unresectable disease was defined by the presence of definite peritoneal disease or extrahepatic metastases other than regional lymph node involvement, extensive bilobar liver metastases or macroscopic para-aortic nodal disease. In the most recent time period (Period 3), patients with liver metastases have not been operated. Vascular invasion was not considered a contraindication to surgical exploration, except in patients aged >60 years with bilateral hepatic artery encasement. Elevated neutrophil : lymphocyte ratios, indicating a potential preoperative host inflammatory response to tumour, were defined as a ratio > 5 and assessed retrospectively using the hospital's haematology records.

Surgical technique

Bile duct excision

All patients underwent a resection of the extrahepatic biliary tree from the level of the upper border of the pancreas to the confluence of the left and right hepatic ducts. If the tumour extended lower than the intrapancreatic portion of the common bile duct, this was also removed and pancreaticoduodenectomy was considered. At the upper end of the biliary tree, the extent of biliary resection has depended on the extent of hepatic resection required and in recent years the technique of 'anatomical' right hepatic trisectionectomy has been adopted when necessary.[9] Recently, routine frozen-section histopathology has also been used to guide the extent of biliary resection. Biliary reconstruction in all patients was performed by antecolic Roux-en-Y hepaticojejunostomy without biliary stents.

Hepatic resection

Hepatic resection was carried out to include all segments of liver involved by tumour or affected by planned loss of vascular supply during surgery. Caudate lobectomy was planned and carried out routinely, except in patients in whom operative difficulties (mainly haemorrhage in the early period) indicated that this would pose an extraordinary risk. In recent years, caudate lobectomy has been performed in all patients. The techniques of right and left hepatic trisectionectomy have been described in detail previously.[10,11]

Vascular resection

Rather than routinely employing the 'no-touch' technique,[5] concomitant portal vein resection and reconstruction have been applied aggressively when macroscopic invasion was suspected at surgery.[12,13] Although some controversial problems remain,[14–16] concomitant hepatic artery resection and reconstruction have

been applied similarly except in patients aged > 60 years. In addition, portal vein arterialization has been considered as an alternative to hepatic artery reconstruction only when the latter was impossible after hepatic artery resection.[17,18] Reconstructions avoided the use of grafts, although a saphenous vein graft was needed to reconstruct a hepatic artery in one case.

Lymphadenectomy

Lymphadenectomy has included lymph nodes, lymphatic channels and nerves surrounding the portal vein and hepatic artery in all patients. In Period 1, lymphadenectomy was regional. In Period 2, it was extended to include para-aortic nodes from the level of the diaphragm to the aortic bifurcation, but this was found to be associated with increased morbidity (mainly ascites requiring diuretics or drainage for several weeks). In Period 3, lymphadenectomy was reduced to include the para-aortic nodes from the level of the coeliac axis to the inferior mesenteric artery in most patients. In elderly patients (aged > 70 years) or patients with significant cardiopulmonary comorbidity, lymphadenectomy has been limited to the regional nodes in an attempt to reduce the risk for perioperative mortality.

Blood transfusion policy

Blood was transfused routinely if the haemoglobin level fell to <8 g/dl. Fresh frozen plasma was transfused if the prothrombin time rose to >30 s. Preoperative blood donation was not used in any of these patients and although a cell saver system is used in our transplant patients, it was not used in this series.

Histopathology

All procedures were performed at the same institution and all specimens were reviewed by the same pathologist. Frozen-section assessment of surgical margins was carried out if there was clinical suspicion of margin involvement at the time of resection in Periods 1 and 2 and routinely in Period 3. Tumours were staged according to the tumour–node–metastasis (TNM) Classification of Malignant Tumours by the International Union Against Cancer (6th edition, 2002) for 'extrahepatic bile duct cancer'.[19] Therefore, intrahepatic metastasis in patients was classified as distant metastasis (including intrahepatic metastasis, peritoneal deposits and positive para-aortic nodes) (M1). R0 resection was defined as negative resection margins and negative radial margins on histology; R1 resection was defined as the histological presence of tumour at any margin, and R2 resection was defined as the macroscopic presence of tumour or M1 disease.

Adjuvant treatment

Only in Period 3 was chemotherapy in the form of capecitabine offered to patients following resection as part of the BILCAP trial.

Follow-up

Patients were followed up in outpatient clinics at 3 and 6 months post-resection and then every 6 months until year 2. Following this, patients attended clinic annually. Patients underwent a CT of the chest, abdomen and pelvis in addition to assessments of tumour markers (CEA [carcinoembryonic antigen] and CA19-9 [carbohydrate antigen 19-9]) and liver function tests at each clinic visit until year 5. Subsequently, clinical examination, tumour markers and liver function tests were carried out annually and CT scans were performed at years 7 and 10. Since 2006, MRI and PET-CT have been used if recurrent disease was suspected on routine follow-up.

Statistical analysis

Continuous variables are presented as the median (range); categorical data are presented as the frequency and proportion (%). Kaplan–Meier survival curves were drawn and log-rank statistics calculated to assess which variables affected survival time. The Cox proportional hazard model was used for multivariate analysis and all variables that were significant or approaching significance ($P < 0.1$) were brought forward for analysis. The Kruskal–Wallis test was used to analyse data for the three time periods. All statistical tests were carried out using SPSS for Windows™ Version 14.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was set at 5%.

Results

Patient characteristics

Between January 1994 and December 2008, 90 patients underwent surgery for PHCCA at St James's University Hospital, Leeds. The surgical resection rate was 92% (83 patients). The 83 resected patients included 48 men and 35 women, with a median age of 57 years (range: 25–81 years). The most common presentation was jaundice; patients without jaundice presented with abdominal pain.

Preoperative patient optimization

In total, 63 (76%) of the 83 resected patients required preoperative biliary drainage. Endoscopic biliary drainage, PTBD, and both EBD and PTBD were carried out in 40 (64%), 14 (22%) and nine (14%) patients, respectively. Of the patients who underwent drainage procedures, 47 (75%) were transferred from district hospitals or other hepatobiliary centres following EBD or PTBD, and two (4%) of these had received metallic stents. Of these 47 patients, 10 required further biliary interventions in Leeds prior to surgery for inadequate relief of jaundice or drainage of planned liver resection segments. Portal vein embolization was used in one patient.

Surgical procedures

Liver resection with caudate lobectomy was carried out in 77 (93%) patients with Bismuth type III or IV lesions. In 55 patients (71% of those undergoing liver resection), a right ($n = 31$) or left ($n = 24$) hepatic trisectionectomy was required (Table 1). Only six patients underwent a bile duct excision for reasons of patient fitness when disease was limited to a Bismuth type I or type II lesion. Portal vein resection and hepatic artery resection were

Table 1 Extent of resection in 83 patients undergoing surgery for perihilar cholangiocarcinoma

Extent of resection	Patients, *n* (%)
Right hepatic trisectionectomy (resection of hepatic segments IV, V, VI, VII, VIII ± I) + bile duct excision	31 (37%) (+pancreaticoduodenectomy in two patients)
Left hepatic trisectionectomy (resection of hepatic segments II, III, IV, V, VIII ± I) + bile duct excision	24 (29%)
Right hemihepatectomy (resection of hepatic segments V, VI, VII, VIII ± I) + bile duct excision	10 (12%) (+segment IVa resection in two patients)
Left hemihepatectomy (resection of hepatic segments II, III, IV ± I) + bile duct excision	11 (13%)
Caudate (segment I) resection alone + bile duct excision	1 (1%)
Bile duct excision alone	6 (7%)
With portal vein resection	32 (39%)
With hepatic artery resection	8 (10%)
With pancreaticoduodenectomy	2 (2%)

required in 32 (39%) and eight (10%) patients, respectively. Of these, seven (8%) patients underwent concomitant portal vein and hepatic artery resection. In two cases, portal vein arterialization was carried out; these patients have been described in detail elsewhere.[18] The median length of the procedure was 390 min (range: 120–630 min).

Tumour characteristics

The median macroscopic tumour size was 25 mm (range: 8–75 mm). R0 resection was achieved in 35 (42%) patients, R1 resection in 39 (47%) patients and R2 resection in nine (11%) patients (liver metastasis, $n = 4$; peritoneal deposits, $n = 2$; paraaortic nodes, $n = 3$). In terms of the histological differentiation of the tumour, well differentiated adenocarcinoma was seen in 37 (45%) cases, moderate differentiation in 21 (25%) and poor differentiation in 25 (30%). Perineural invasion was seen in 72 (89%) patients. Two (2%) patients had stage T1 disease, 35 (43%) had T2, 31 (38%) had T3 and 13 (16%) had T4 disease. Lymph node infiltration was noted in 47 (57%) patients.

Morbidity and mortality

A total of 70 complications occurred in 52 (64%) patients (Table 2). The rate of mortality was 7% (six patients): five deaths followed episodes of sepsis related to liver insufficiency which progressed to multi-organ failure, and the sixth patient died following a massive abdominal haemorrhage related to MRSA (methicillin-resistant *Staphylococcus aureus*) sepsis with the development of a hepatic artery aneurysm. The median length of stay was 18 days (range: 5–137 days).

Table 2 Morbidity in 83 patients undergoing surgery for perihilar cholangiocarcinoma

Complication	*n* (%)
Transient hepatic insufficiency	13 (16%)
Sepsis	12 (14%)
Wound infection	10 (12%)
Haemorrhage	9 (11%)
Bile leak	8 (10%)
Transient renal failure	5 (6%)
Gastrointestinal haemorrhage	3 (4%)
Chest infection	2 (2%)
Portal vein thrombosis	1 (1%)
Others	7 (8%)

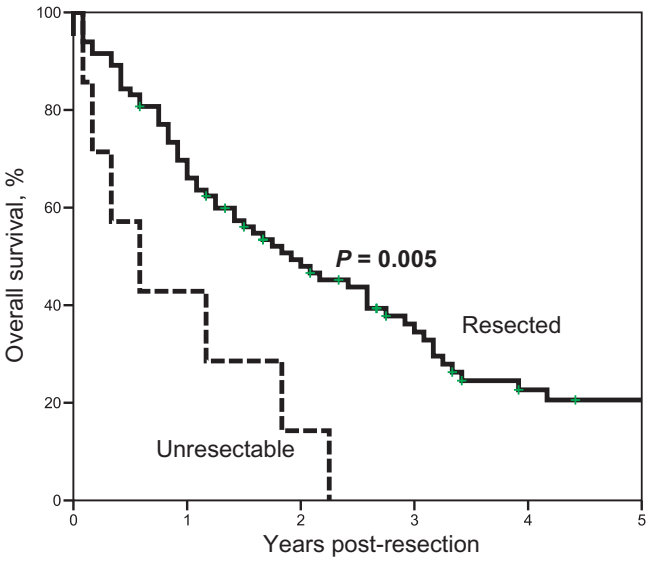

Figure 1 Kaplan–Meier curves for overall survival in resected and unresected patients

Table 3 Overall survival in 90 patients with perihilar cholangiocarcinoma: numbers at risk

	Years					
	0	1	2	3	4	5
Resected	83	57	36	21	11	9
Unresectable	7	3	1	–	–	–

Survival

Figure 1 and Table 3 show overall survival and numbers at risk in this series of patients compared with that in those patients

Table 4 Clinicopathological features predicting overall survival

Variable	Patients, *n*	5-year survival, %	Median survival, months	Univariate analysis, *P*-value	Multivariate analysis, RR (95% CI)	Multivariate analysis, (*P*-value)
Male	48	17	22	0.494		
Female	35	25	24			
Age < 60 years	48	19	23	0.906		
Age > 60 years	35	20	22			
PTBD	23	6	20	0.095	**2.27 (1.18–4.38)**	**0.015**
No PTBD	56	29	26		**1.00**	
ERCP	49	15	18	0.676		
No ERCP	30	25	26			
Trisectionectomy	55	21	20	0.397		
No trisectionectomy	28	15	31			
Size > 25 mm	36	**8**	**13**	**<0.001**	1.00	0.133
Size < 25 mm	39	**31**	**38**		1.90 (0.82–4.41)	
R0 resection	38	**33**	**31**	**0.042**	0.59 (0.32–1.07)	0.083
R1/R2 resection	45	**8**	**18**		1.00	
Distant metastasis	9	**0**	**7**	**0.001**	**2.77 (1.04–7.35)**	**0.040**
No distant metastasis	74	**23**	**25**		**1.00**	
Well differentiated	37	**27**	**31**	**0.038**	0.56 (0.27–1.16)	0.121
Moderately/poorly differentiated	46	**14**	**13**		1.00	
Portal vein resection	32	**9**	**12**	**0.013**	1.21 (0.63–2.32)	0.572
No portal vein resection	51	**28**	**31**		1.00	
Hepatic artery resection	8	12	11	0.387		
No hepatic artery resection	75	20	25			
Microscopic direct vascular invasion	42	**12**	**17**	**0.009**	1.34 (0.67–2.66)	0.409
No microscopic direct vascular invasion	40	**30**	**35**		1.00	
Perineural invasion	72	18	22	0.186		
No perineural invasion	9	44	38			
Positive lymph node invasion	47	**13**	**15**	**0.015**	1.85 (0.99–3.46)	0.053
Negative lymph node invasion	35	**32**	**36**		1.00	
Complications	52	20	18	0.350		
No complications	29	22	29			
T-stage ½	37	**36**	**38**	**<0.001**	0.72 (0.30–1.74)	0.459
T-stage ¾	44	**9**	**13**		1.00	
Blood transfusion	48	**14**	**15**	**0.009**	**2.00 (1.09–3.69)**	**0.026**
No transfusion	35	**27**	**35**		**1.00**	
Neutrophil : lymphocyte ratio < 5	39	**24**	**20**	0.427		
Neutrophil : lymphocyte ratio > 5	27	**18**	**16**			

Data in bold are significant at $P < 0.05$.
RR, relative risk; 95% CI, 95% confidence interval; PTBD, percutaneous transhepatic biliary drainage; ERCP, endoscopic retrograde cholangiopancreatography.

deemed inoperable. The median length of follow-up was 20 months (range: 0–168 months). Overall survival was 70% at 1 year, 36% at 3 years, 20% at 5 years and 11% at 10 years following surgical resection. The clinicopathological factors influencing overall survival are shown in Table 4. Significant predictors of decreased overall survival on univariate analysis were tumour size >25 mm ($P < 0.001$), lack of R0 resection ($P = 0.042$), presence of distant metastasis ($P = 0.001$), moderate or poor tumour differentiation ($P = 0.038$), requirement for portal vein resection ($P = 0.013$), microscopic direct vascular invasion ($P = 0.009$), positive lymph nodes ($P < 0.001$) and requirement for blood transfusion ($P = 0.009$). The use of PTBD only approached significance on univariate analysis ($P = 0.095$).

Significant predictors of decreased overall survival on multivariate regression were presence of distant metastasis (relative risk [RR] 1.04–7.35; $P = 0.040$), use of PTBD (RR 1.18–4.38; $P = 0.015$) and requirement for blood transfusion (RR 1.18–4.38; $P = 0.015$) (Fig. 2, Table 5).

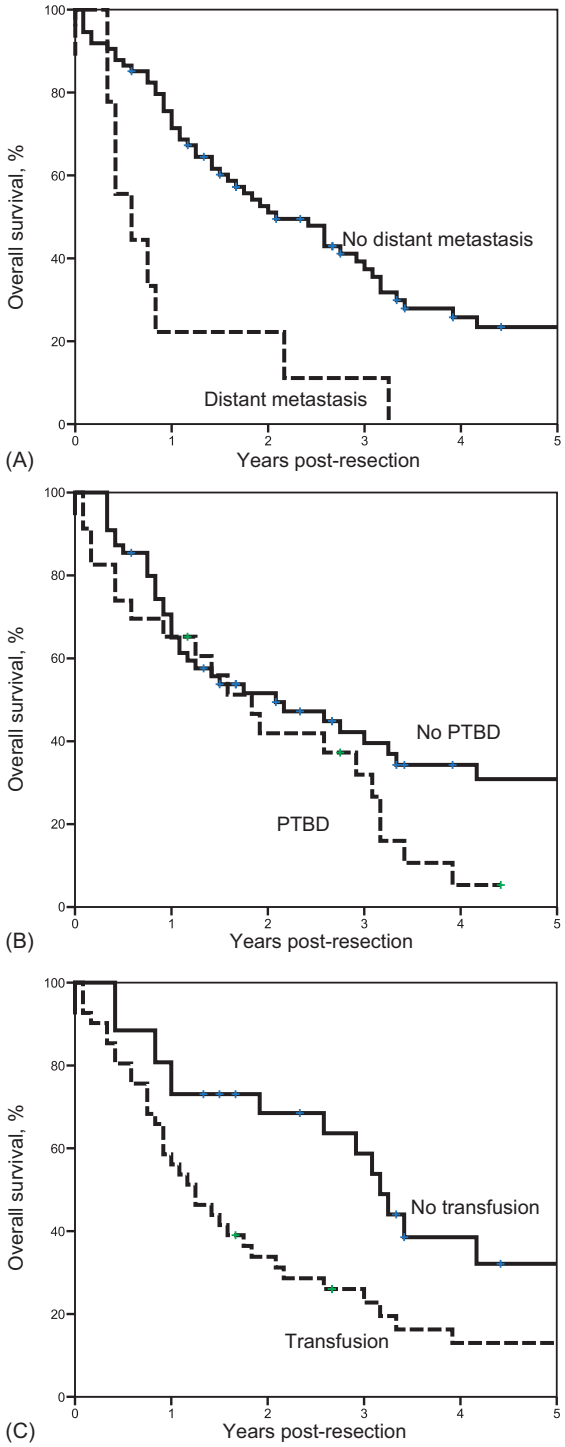

Figure 2 Survival curves according to (A) distant metastasis (multivariate analysis, $P = 0.040$; hazard ratio [HR] 2.27, 95% confidence interval [CI] 1.04–7.35), (B) percutaneous transhepatic biliary drainage (PTBD) (multivariate analysis, $P = 0.015$; HR 2.27, 95% CI 1.18–4.38) and (C) blood transfusion requirement (multivariate analysis, $P = 0.026$; HR 2.00, 95% CI 1.09–3.69)

Table 5 Survival analyses in 83 patients undergoing resection for perihilar cholangiocarcinoma according to distant metastasis, percutaneous transhepatic biliary drainage (PTBD) and blood transfusion requirement: numbers at risk

	Years					
	0	1	2	3	4	5
(A)						
No distant metastases	74	55	34	21	11	9
Distant metastases	9	2	2	1	–	–
(B)						
PTBD	23	15	8	6	1	–
No PTBD	56	39	25	16	10	9
(C)						
No blood transfusion	26	21	15	12	6	4
Blood transfusion	41	24	13	8	4	4

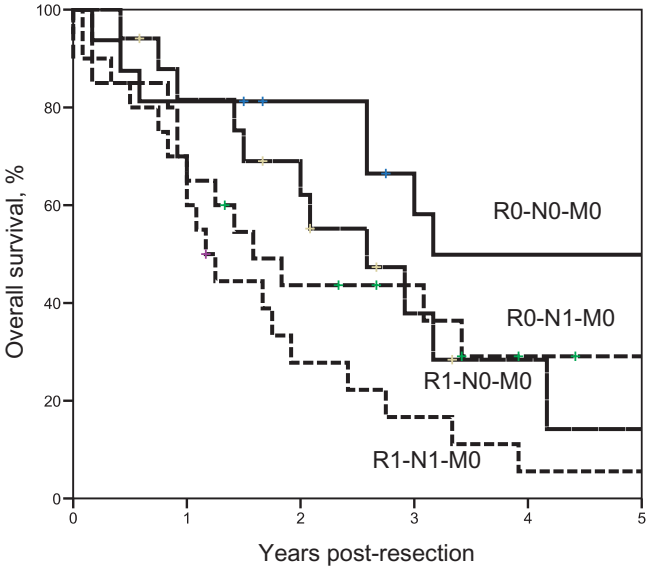

Figure 3 Subgroup analysis by resection status, lymph node status and presence of distant metastasis. R0, microscopic curative resection; R1, macroscopic curative resection; R2, macroscopic non-curative resection; M0, absence of distant metastasis; M1, presence of distant metastasis; N0, absence of lymph node metastasis; N1, presence of lymph node metastasis

Subsequently, presence of distant metastasis, lymph node status and margin status were used to stratify the patient group into four groups, survival curves for which are shown in Fig. 3, Table 6. Patients with R0-M0 with negative lymph nodes (R0-M0-N0) achieved a 5-year survival rate of 49% (Fig. 3).

Comparison of outcomes in the three time periods

The clinicopathological differences observed among the three different time periods (Period 1, 1994–1998; Period 2, 1999–2003; Period 3, 2004–2008) are shown in Table 7. Although we insti-

Table 6 Subgroup analysis by resection status, lymph node status and presence of distant metastasis: numbers at risk and overall survival

	Numbers at risk at years:					
	0	1	2	3	4	5
R0-N0-M0	16	13	11	8	6	6
R0-N1-M0	19	14	8	6	2	1
R1-N0-M0	17	13	10	4	2	1
R1-N1-M0	21	15	6	3	1	1
	Overall survival at:					
	1 year	**3 years**	**5 years**			
R0-N0-M0	81	66	49	$P = 0.195$	$P = 0.089$	
R0-N1-M0	68	41	25			
R1-N0-M0	82	38	14	$P = 0.144$	$P = 0.264$	
R1-N1-M0	71	20	7			

R0, microscopic curative resection; R1, macroscopic curative resection; R2, macroscopic non-curative resection; M0, absence of distant metastasis; M1, presence of distant metastasis; N0, absence of lymph node metastasis; N1, presence of lymph node metastasis.

gated no major differences in operative procedures across the three periods, we succeeded in reducing the rate of perioperative blood transfusion requirement from 89% in Period 1 to 33% in Period 3 ($P < 0.001$). The postoperative mortality rate in Period 3 (6%) was lowest. In terms of tumour characteristics, only the frequency of patients with distant metastasis decreased significantly period by period ($P = 0.022$). The rates of R0 resection in Periods 1, 2 and 3 were 39%, 52% and 44%, respectively.

Survival curves for the three periods are shown in Fig. 4 (Table 8). The number of resected patients doubled between Periods 1 and 3, from 18 to 36. Five-year survival rates for Periods 1, 2 and 3 were 22%, 14% and 25%, respectively. Period 3 showed the best survival, although the degree of improvement did not reach statistical significance (Periods 1 vs. 3, $P = 0.225$; Periods 2 vs. 3, $P = 0.108$; Periods 1 vs. 2, $P = 0.579$). However, it should be noted that 1-year survival post-surgery significantly improved from 50% in Period 1 to 62% in Period 2 and 86% in Period 3 (Kruskal–Wallis test, $P = 0.030$).

Discussion

Surgical resection of PHCCA remains a formidable surgical challenge and our overall results are comparative with those of other large Western series.[20–25] An aggressive surgical approach was employed, similar to that seen at Nagoya University Graduate School of Medicine, which has the greatest degree of experience in the management of PHCCA of anywhere in the world.[26] In terms of prognostic factors, the results reported here are similar to those of the Nagoya experience in that on univariate analysis they show that R0 status, lymph node invasion, presence of distant metastasis, portal vein invasion, histological grade and microscopic direct vascular invasion are important in determining outcome.[27] The rate of resectability in the current series (92%) is relatively high compared with those reported in other series.[28] However, this comparison is not always useful because preoperative workup protocols and staging investigations differ among units.

There is some concern that the rate of R0 resection has not significantly increased over time, but this may reflect the fact that resection is more often attempted in patients with more locally advanced disease as experience increases. The pursuit of R0 resections must be balanced against the need to offer surgery to all patients for whom it might have potential benefit and to carry out extensive resections safely. The increased use of intraoperative frozen-section histopathology may allow us to improve the R0 resection rate. However, there have been reports that frozen sections can be misleading[29] and extending resections in accordance with the indications of frozen sections may not improve outcomes.[27] Many Eastern centres, including that in Nagoya, advocate portal vein embolization as a useful adjunct to surgery to improve postoperative outcomes following extended resection for PHCCA, perhaps allowing more extensive resection to ensure negative resection margins.[30] As yet, no data from randomized trials are available, but the majority of patients in this series presented with lobar atrophy caused by vascular invasion and thus portal vein embolization was not thought to be beneficial. The histological grade of resected tumours appears to represent another area of difference between the series reported from, respectively, our unit and that at Nagoya. Poor tumour differentiation was observed in 30% of resected patients in the present series, but in only 7% of patients reported in a recent series from Nagoya.[4] More detailed analysis is required to assess whether there is a significant difference in tumour grade in patients presenting to Eastern and Western centres as tumour grade has been shown to significantly affect longterm outcomes.[4,23,31]

The finding that PTBD significantly impaired overall survival on multivariate analysis has not emerged before in a Western series, although it was recently described in two Eastern series.[32,33] Preoperative biliary drainage is advocated prior to resection for PHCCA as it reduces complications that arise from major resections in cholestatic livers.[34] However, PTBD carries a significant risk for direct tumour seeding to intrahepatic, peritoneal and even pleural sites, all of which we have seen.[35–38] Percutaneous transhepatic biliary drainage can also directly result in portal vein thrombosis, although this seems comparatively rare and was not seen in this series.[39] The data demonstrate that PTBD is an independent predictor of a poor outcome; it is unclear whether this is simply the result of tumour seeding or whether other factors may be implicated. More recently, evidence from a retrospective series published by the Hokkaido University Graduate School of Medicine, Sapporo, Japan suggested that, not only is PTBD harmful, but nasobiliary endoscopic drainage has advantages over EBD.[33] These include decreased stent occlusions, decreased episodes of cholangitis and increased diagnostic accuracy if complications arise.[33] Endoscopic biliary drainage may increase the risk for

Table 7 Clinicopathological differences in patient data among three time periods

Variable	Period 1 1994–1998, % (n = 18)	Period 2 1999–2003, % (n = 29)	Period 3 2004–2008, % (n = 36)	Kruskal–Wallis, P-value
Male	56	52	64	0.603
Age < 60 years	44	31	50	0.303
Percutaneous transhepatic biliary drainage	12	48	21	0.076
Endoscopic retrograde cholangiopancreatography	88	52	60	0.058
Trisectionectomy	61	72	64	0.786
Portal vein resection	33	41	39	0.859
Hepatic artery resection	6	10	8	0.407
Operation time, mins, median (range)	330 (240–480)	395 (165–540)	390 (120–630)	0.835
Blood transfusion	**89**	**69**	**33**	**<0.001**
Complications	56	61	71	0.470
Elevated neutrophil : lymphocyte ratio	33	57	33	0.191
Postoperative mortality	11	7	6	0.727
Postoperative stay, days, median (range)	17 (8–24)	17 (10–59)	23 (5–137)	0.171
Size > 25 mm	50	56	43	0.657
Well differentiated	50	52	36	0.399
Microscopic direct vascular invasion	56	36	61	0.123
Perineural invasion	88	93	86	0.696
T-stage ½	56	68	43	0.143
Positive lymph nodes (N1)	50	57	61	0.741
Distant metastasis (M1)	**28**	**10**	**3**	**0.022**
R0 resection	39	52	44	0.679
Median survival, months	11	17	31	0.716

Data in bold are significant at $P < 0.05$.

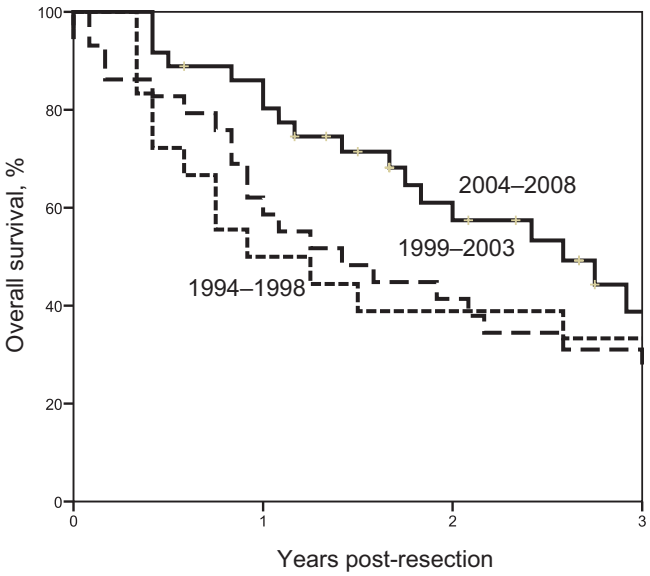

Figure 4 Kaplan–Meier survival curves for the three time periods analysed. Period 1: 1994–1998; Period 2: 1999–2003; Period 3: 2004–2008. Periods 1 vs. 2: $P = 0.579$; Periods 1 vs. 3: $P = 0.225$; Periods 2 vs. 3: $P = 0.108$

Table 8 Survival data for Periods 1, 2 and 3: numbers at risk

	Years			
	0	1	2	3
1994–1998	18	9	7	6
1999–2003	29	18	12	9
2004–2008	36	30	17	7

cholangitis, which impairs hepatic regeneration post-resection,[33] but this was not seen in our series, in which the main issues referred to difficulty in duct cannulation and potential risk for pancreatitis. These issues can only be addressed by a randomized controlled trial, but this would be difficult to carry out. Thus, until further data are available, we will continue to use EBD as a first-line biliary drainage procedure as part of our protocol. As the majority of our patients undergo EBD and/or PTBD prior to referral, this factor is currently outwith our control. This suggests that national guidelines should be updated to improve overall patient management because there are currently no clear recommendations.[40]

Our investigation indicated that blood transfusion requirement is an independent indicator of a poor prognosis following surgical

resection for PHCCA. However, this has been reported previously in a smaller series in which it was found to be significant only on univariate analysis.[41] In other malignancies, transfusion requirement is thought to worsen oncological outcomes, probably as a result of the immunosuppressive effect of transfused blood products.[41] Hence, the significant reduction in the level of requirement for blood transfusion in the most recent time period, which is probably attributable to our increase in experience, can only benefit patient outcomes.

Survival analyses revealed that, in the M1 group, surgery achieved very poor survival at a rate similar to that in unresectable patients. In addition, survival analyses according to lymph node metastasis in patients with M0 disease who underwent R0 or R1 resection demonstrated that the R0-N0-M0 group achieved excellent survival (5-year survival rate: 49%) and the R1-N0-M0 group did less well. Survival rates in the R0-N1-M0 and R1-N1-M0 groups were only 25% and 7%, respectively (Fig. 3). These results show that surgery alone may be insufficient to conquer PHCCA with lymph node metastasis, even if R0 resection can be achieved.

Previous reports have identified both an elevated neutrophil : lymphocyte ratio and the presence of postoperative complications as important factors affecting survival in colorectal liver metastasis (CLM).[42,43] However, in the analysis shown here, elevation of the neutrophil : lymphocyte ratio, indicating a potential preoperative inflammatory response to tumour, did not affect survival in PHCCA. This may be because the neutrophil : lymphocyte ratio in PHCCA can also be increased by cholestasis and/or cholangitis. In addition, analyses of postoperative morbidity demonstrated that postoperative complications had no influence on survival in PHCCA. This may reflect the fact that postoperative complications occur more frequently in PHCCA patients than in patients undergoing hepatic resection for CLM.

One-year survival rates significantly increased over the three time periods (from 50% to 86%), as did median survival times (from 11 to 37 months) in response to an evolution in practice. In Period 1, patients often presented at a late stage, which, combined with our relatively low experience, contributed to poorer results. By the intermediate period (Period 2), it was clear that aggressive resection would lead to improved outcomes. Most recently (Period 3), as our approach has matured and patient selection has improved, the best results have become apparent. This can be measured by the lower postoperative mortality and higher 1- and 5-year survival rates. It is also of note that our unit has seen no postoperative mortality since 2004. In addition, although we continue to carry out predominantly hepatic trisectionectomy with extensive lymph node dissection and increasingly complex vascular reconstructions, requirements for blood transfusion are significantly reducing with experience, in line with decreases observed in major Eastern centres.[26,43,44]

Although the body of literature describing results following surgical resection for PHCCA is increasing, even the largest hepatobiliary centres have considerably less experience in this area than they do in other diseases, such as CLM or hepatocellular carcinoma (HCC). During the 15-year period reported here, 1300 patients with CLM and 140 patients with HCC underwent surgical resection at St James's Hospital, compared with only 83 with PHCCA. This fact and the clear surgical learning curve that is apparent in the results presented here support the centralizing of resources for PHCCA surgery.[45] In addition, access to newly available knowledge is important in the management of PHCCA. Therefore, four senior surgeons from Nagoya University Graduate School of Medicine, including two of the present authors (TI and YS), have been appointed as clinical researchers at Leeds since 2003, and the management of patients with PHCCA has been subject to much discussion. The present data suggest that further reductions in blood transfusion requirements and the avoidance of PTBD will continue to improve results. The next main challenge in maximizing outcomes of PHCCA patients will refer to increasing the rate of R0 resection. This can probably only be achieved by earlier diagnosis and referral, although the introduction of an effective neoadjuvant therapy may help. In addition, improved preoperative staging, which may be supported by the advent of PET-CT,[46] should ensure that only patients in whom benefit can be achieved undergo this major surgical intervention.

In summary, we have identified that blood transfusion requirement and preoperative percutaneous biliary drainage represent independent indicators for a poor prognosis following resection of PHCC and thus are areas for potential improvement. Longterm survival can be achieved following aggressive surgical resection of this tumour, but it is apparent that these patients should be managed in high-volume centres in order to improve their outcomes.

Conflicts of interest

None declared.

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